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Shaping the operations research agenda for antiretroviral-based prevention products for women: Gels and rings

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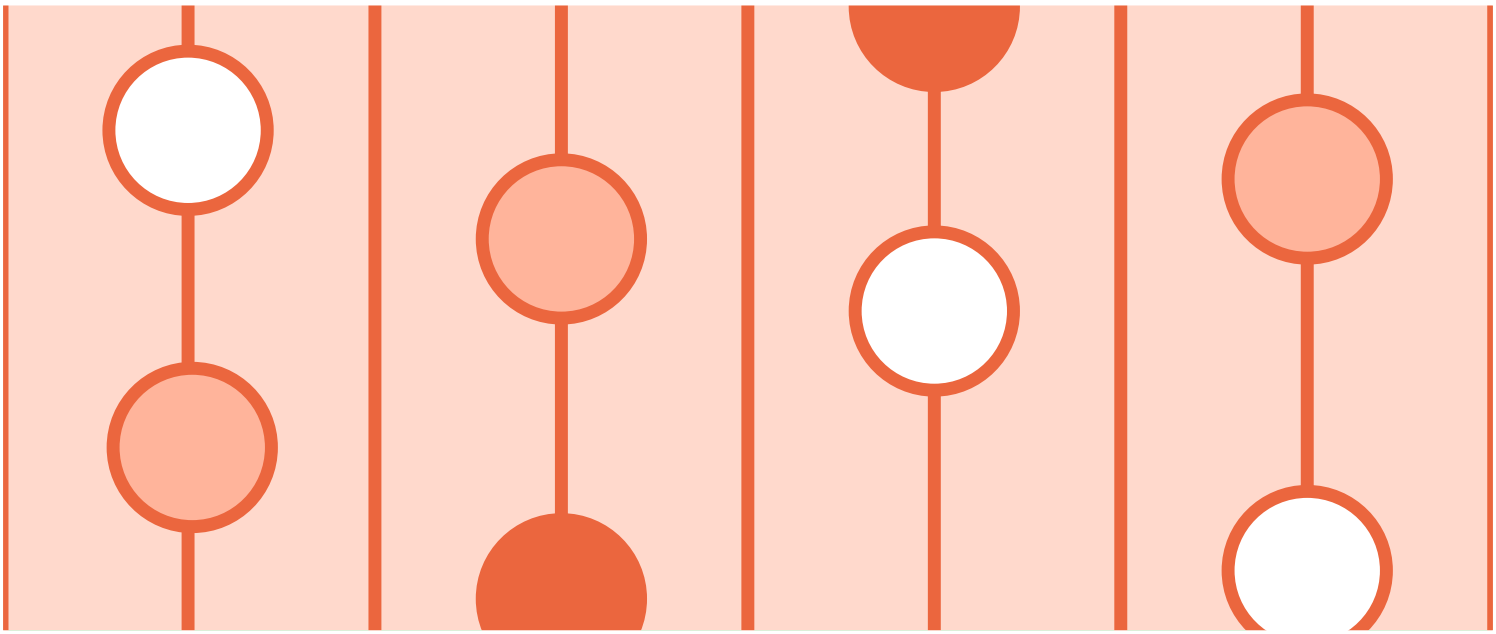
SHAPING THE OPERATIONS RESEARCH AGENDA FOR ANTIRETROVIRAL-BASED PREVENTION PRODUCTS FOR WOMEN: GELS AND RINGS

Consultation Report



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USAID
FROM THE AMERICAN PEOPLE

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ACRONYMS

ANC	antenatal care
ARV	antiretroviral
CBR	Population Council's Center for Biomedical Research
EC	emergency contraception
FC	female condom
FP	family planning
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
MCH	maternal and child health
OR	operations research
PHC	primary health care
PICOT	Population, Intervention, Comparison or Control, Outcome, and Time
PMTCT	prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
RH	reproductive health
USAID	U.S. Agency for International Development
VCT	voluntary counseling and testing
WHO	World Health Organization

BACKGROUND AND RATIONALE

The HIV prevention research field has yielded a number of important new approaches during the last several years, including medical male circumcision, oral pre-exposure prophylaxis (PrEP), and treatment as prevention. Together with male and female condoms, prevention of mother-to-child transmission (PMTCT), and antiretroviral (ARV) treatment, these interventions have the potential to help decrease the rate of new HIV infections and begin to curb the epidemic overall. At the same time, the need for women-centered products remains. Clinical effectiveness trials are under way for 1 percent tenofovir gel and the dapivirine ring, and research on other ARV-containing gels and rings continues. Given the urgent need for these products, the groundwork for introduction and rollout is being laid in parallel with clinical research.

The Population Council, in collaboration with U.S. Agency for International Development (USAID) and other partners, is engaged in a program of research and action to prepare for the successful introduction of women-centered ARV-based HIV prevention methods. Following the results of the CAPRISA 004 trial, which demonstrated that tenofovir gel reduced the risk of HIV infection, USAID outlined a "Shared Vision"[1] for access to microbicides that included development of an operations research agenda as one of its elements.

Developing such an operations research (OR) agenda to prepare for the introduction of a new product is an important but often overlooked step. Clinical trials assess the safety and efficacy of medical interventions in tightly controlled settings; as such, they are not designed to address critical questions related to service provision under routine circumstances. Operations research generally identifies health system and service delivery issues and tests programmatic options for program managers and policymakers to consider when designing approaches to introduce or expand access to a product.

To help shape this agenda, the Population Council drew on its long experience and expertise in microbicide product development and testing, as well as operations research in developing countries for family planning, reproductive health, and HIV/AIDS, all potential systems for microbicide delivery.[2] Given that numerous other efforts are under way to address the delivery of oral Truvada for PrEP, and that clinical research on rectal microbicides is in earlier phases, this meeting focused specifically on gels and rings for vaginal use. While recognizing the significance of other biomedical interventions (such as male circumcision, oral PrEP, and treatment as prevention), the need for women-centered products remains critical. Making these products available requires a wide range of activities in areas including clinical testing, regulatory strategy, licensure, manufacturing, and financing. While all are key to delivering products, this meeting focused specifically on an operations research agenda for gels and rings.

[1]USAID Proposal for a Shared Vision and Strategic Plan for Microbicide Introduction, May 24, 2011. http://transition.usaid.gov/our_work/global_health/aids/TechAreas/research/strategic_plan_microbicide_introduction.pdf.

[2]See, for example, Fisher, Andrew A. and James R. Foreit. 2002. *Designing HIV/AIDS Intervention Studies: An Operations Research Handbook*. New York: Population Council.

MEETING PARTICIPANTS, AGENDA, FORMAT

The two-day meeting (17–18 June 2012) drew together nearly 40 diverse participants, with approximately half coming from a number of countries in Africa or India. Participants' expertise spanned operations research, microbicide clinical research and product development, AIDS care and services, policy and program implementation, and social and behavioral research. Council staff drew on their experience and a review of key documents and tools (see Appendix 1) to develop a list of potential operations research questions across a number of domains (see Appendix 2). Some of these questions are discussed more fully later in the report. To engage meeting participants with the issues and get an initial sense of priority and timing, the questions were sent to participants prior to the meeting for their feedback.

Given the complexity and rapid evolution of the ARV-prevention landscape and the product pipeline, the first part of the meeting was devoted to reviewing recent results and developments in clinical testing, product development, acceptability, and regulatory review. Speakers also offered insights and analysis on lessons from other product introduction efforts, outlined the Population, Intervention, Comparison or Control, Outcome, and Time (PICOT) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) processes used by the World Health Organization (WHO) in weighing evidence to develop guidance, and offered a primer on operations research approaches, including highlighting the types of questions that OR can—and cannot—address.

During lively discussion and debate, meeting participants worked to identify priority OR issues and began to outline how studies could be designed to address these questions. These discussions took place in the larger group as well as in breakout sessions where small groups identified key issues for the different technologies (gels and rings) and then outlined approaches to operations research on several priority topics. This report highlights the main themes identified in the presentations and discussions, and outlines ideas generated for priority research topics and approaches.

WOMEN AND HIV PREVENTION: WHAT WORKS?

The meeting began with an overview of biomedical, behavioral, and structural interventions currently available to women to reduce their risk of HIV infection. A comprehensive review of evidence on "what works for women" (www.whatworksforwomen.org) undertaken by the Futures Group notes a number of strategies to help women prevent HIV, including male and female condom use, reducing the number of partners, and treatment for sexually transmitted infections. Treatment as prevention also offers a promising new approach, though questions remain about its implementation in resource-limited settings.[3] The review also notes that pre-

[3]Based on recent research and resulting regulatory and policy guidance, pre-exposure prophylaxis may also provide an important prevention strategy for women. However, it is not yet included in www.whatworksforwomen.org.

vention efforts for married women have been neglected, although married women may be at increased risk of HIV. The review suggests that efforts be increased to meet women's reproductive health needs, including increasing condom use, sexuality education and communication, especially among young people. Overall, it highlights the limitations of approaches currently available and the need for more biomedical and structural tools, options, and approaches to empower women to help prevent HIV. The review underscores the importance of the consultation as part of efforts to develop and make rapidly available gels, rings, and other new technologies for women.

LESSONS FROM OTHER HEALTH TECHNOLOGIES

Experience with introducing other health technologies provides a number of useful lessons that can be applied to ARV-based prevention for women, although no existing product offers a precise model. A number of lessons can be drawn from emergency contraception, contraceptive vaginal rings, the female condom, HPV vaccine, and HIV treatment. Overall, across time, setting, and products, women's overarching questions about new reproductive health technologies, including those for HIV prevention, are relatively straightforward and center on whether a product **works**, whether it **causes harm** (to the woman, her partner, or her baby), whether it will **jeopardize future fertility**, and whether it will disrupt her **relationship** with her partner.

Although women's unmet need for modern contraception may appear to be attributable to problems with access, a 2011 analysis showed several other issues as central: concerns about health or side effects, opposition from the woman or her partner, and infrequent sex.[4] This may suggest that coitally dependent products could fill an important niche, in contrast with concerns that women will struggle to use such products consistently.

Emergency contraception (EC) shares a number of attributes with peri-coital gel use: both are user initiated, time sensitive, and require information and understanding to be used effectively. Women use EC even when other highly effective contraceptive products are available, and express interest in peri-coital methods. Although emergency contraception continues to be stigmatized in many settings, women still want it and generally prefer to have on-demand pharmacy access. Multiple brands are on the market in different settings, suggesting both a continued "unmet need" and its commercial viability. Finally, while making EC available without a prescription has expanded access, such availability does have its downsides, making it difficult to monitor product safety and quality and to provide counseling. It also requires that women have funds available to purchase the product.

Contraceptive vaginal rings can offer some clear lessons and parallels for ARV-containing rings. Protocols and duration of use vary among rings currently on the market which include

[4]Darroch, Jacqueline E., Guilda Sedgh, and Haley Ball. 2011. *Contraceptive Technologies: Responding to Women's Needs*. New York: Guttmacher Institute.

monthly and three-month rings. While such rings do not require action daily or at the time of sex, they do require user effort. Experience with rings dates back decades, but most data is from the US and Europe and there is a need both to mine and perhaps generate more data on women's experience with rings in a variety of settings. One important issue is expulsion and slippage among women with different reproductive histories, which needs to be documented and proactively addressed with users.

The **female condom** (FC) is often cited as an important example for microbicide introduction and there are clear parallels and lessons from this coitally related, user- dependent, vaginally inserted method. The female condom was subject to strong provider and policymaker bias, which, coupled with relatively high production costs, resulted in a cycle of low demand and high cost. Like the gels and rings being developed for vaginal use, the FC is not a perfect product. Many women can and do use the FC, however, especially if they are supported as they become accustomed to and experienced with it; user education includes communication and negotiation skills and information on sexuality and anatomy. Consistent use, while optimal, is difficult for many women to achieve, suggesting that HIV prevention products should ideally be provided together as a range of options so users can choose and switch among strategies to maximize their overall protection.

Finally, efforts to introduce ARV-based gels and rings should be informed by the extraordinary global efforts to roll out **HIV treatment and care**. Maintaining adherence for any health intervention over time is challenging, and it is important that program approaches acknowledge that incomplete adherence is normative for both treatment and prevention while at the same time developing, testing, and implementing approaches to bolster adherence. HIV testing is the gateway for use of ARV-based prevention and for antiretroviral therapy, and both approaches will require medical monitoring. All of the issues outlined above have implications for determining which service-delivery settings will be feasible, the periodicity of testing and resupply, what types of provider will be permitted to deliver the service, and scalability.

These examples and others underscore that product introduction efforts need to demonstrate that health systems and providers have the **capacity** to deliver the product safely and effectively; that the product and program are **affordable and acceptable** to users, programs, and funders; and that key (and potentially diverse) user groups can **access and use** the product as well as the program that delivers it. A vision needs to be presented for how a given product (such as tenofovir gel or the dapivirine ring) fits into the overall HIV prevention landscape globally and in specific settings, and satisfactory answers must be developed to address any concerns.

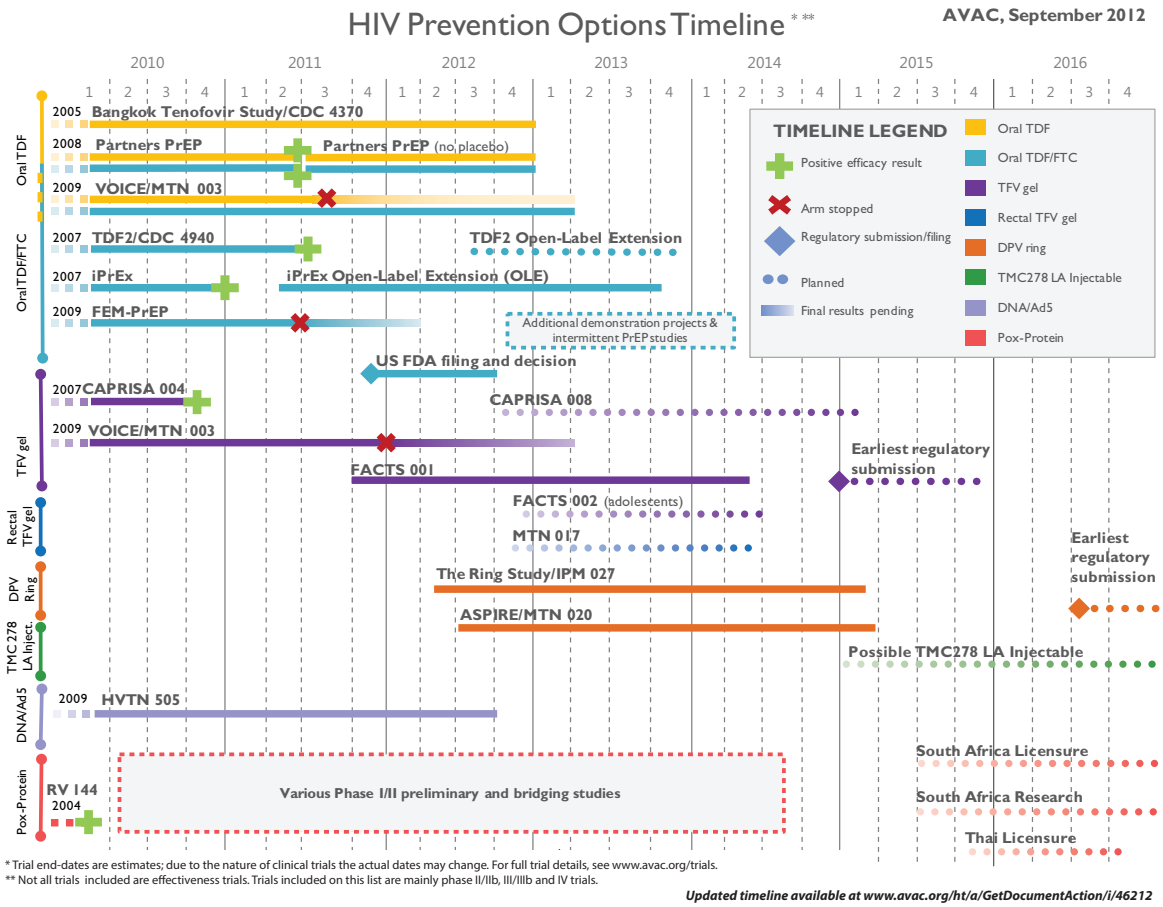
Drawing on a number of analyses, including a previous Council meeting and publication on this topic,[5] the relevant lessons and insights that can be applied to microbicide introduction are relatively clear and can inform operations research and program design for delivering ARV-based gels and rings without a great deal of additional analysis. Incorporating these lessons into program design will require vision, commitment, and investment.

[5]Brady, Martha, and Elizabeth McGrory. 2007. "*Insights and evidence from product introduction: Lessons for microbicides*," *Day of Dialogue.* New York: Population Council.

WHERE ARE WE WITH MICROBICIDES?

Product pipeline and lead products

A review of the microbicide pipeline provided background information on the status of various product leads, focusing on 1 percent tenofovir gel and the dapivirine ring, the products furthest along in development. FACTS 001, a safety and effectiveness trial of 1 percent tenofovir gel, is currently under way in South Africa with results expected in 2014. Two effectiveness trials of 1 percent tenofovir gel have been conducted, with one showing a 39 percent reduction in risk of HIV acquisition (CAPRISA 004) and the other showing no effect (VOICE). A different formulation of 1 percent tenofovir gel is also being developed for rectal use. Two safety and effectiveness trials of the dapivirine ring, a sustained-release device, are expected to report results in 2015 (ASPIRE and the Ring Study). For both of these lead products, additional studies will provide data on safety during pregnancy and when breastfeeding, use in adolescents, drug interactions, manufacturing, and other issues necessary for licensure. The Population Council, CONRAD, and other groups continue research and development on other product leads, some of which are also multipurpose prevention technologies designed to also act as contraceptives.



* Trial end-dates are estimates; due to the nature of clinical trials the actual dates may change. For full trial details, see www.avac.org/trials.
** Not all trials included are effectiveness trials. Trials included on this list are mainly phase II/IIb, III/IIIb and IV trials.

Updated timeline available at www.avac.org/ht/a/GetDocumentAction/i/46212

This timeline suggests that ARV-based gels and rings will be introduced into an increasingly dynamic and complex environment of prevention approaches with implications for service delivery, user education and action, and investment.

Acceptability and use

Ongoing product development for gels and rings for HIV prevention has been accompanied and informed by acceptability research at all phases of preclinical and clinical development. This research has been conducted within and outside of clinical trials. Acceptability research to date indicates that overall women are quite positive about the products being tested and that although different women have different preferences, all delivery forms are acceptable. Some women are interested in using a product without telling their partner(s), although involving male partners is important for some women and in some settings. Cultural norms including those for "tight" or "dry" sex have not negatively affected acceptability, and in fact many women in trials (and their partners) report that microbicide gels make sex more comfortable and pleasurable. Acceptability needs to be assessed and addressed for providers, policymakers, and other key decisionmakers as well as users. Important dimensions for acceptability go beyond basic product characteristics and include issues like storage and disposal.

Clinical trials offer a critical opportunity to learn about acceptability, and rich datasets exist from completed clinical trials as well as those being generated in ongoing trials. Additional information may be available from research and from the introduction of related technologies like contraceptive vaginal rings. In many cases, these data have not been thoroughly analyzed or applied, and they should be exploited to frame further studies and inform any future introduction efforts. At the same time, it is unclear how findings from trials will translate to ongoing use in routine service settings, so further research may be needed to assess dimensions of acceptability as products are phased into wider use.

OPERATIONS RESEARCH: WHAT IT CAN AND CANNOT DO

A review of operations research underscored that while there is some fluidity in definitions, parameters, and terminology, in general OR looks at the *health system* as the unit of analysis and seeks to measure outcome indicators for service delivery that are meaningful for program design, budgeting, and management. OR generates evidence to guide policy, programming, and budgeting for service delivery, and different types of research are needed to generate different types of evidence. OR produces evidence on issues like the delivery attributes for the provider, system, and user; system requirements and functioning for effective service delivery; parameters for policy support and delivery; and commodities logistics, cost, and prices. As such it complements research that is biomedical, clinical, or oriented to user behavior and acceptability. At the same time, not all problems or questions related to service implementation need to be addressed by research-based evidence, and it is important to ensure that research approaches match the questions they are seeking to address.

Operations research studies need to clearly define and understand potential audiences and how they would use the evidence generated, as well as the systems adjustments needed for introducing and implementing any operational changes indicated by the OR findings. Specific questions can be addressed through nested studies and multisite studies, as the OR itself

should not be disaggregated into too many smaller, discrete studies. Developing OR should involve the end users of the research (for example, the Ministry or system responsible for implementation) and should include both plans *and budget* for extended actions beyond the study period to support institutionalization and scale-up of activities indicated by research evidence. Given this, the cycle for an OR project can often stretch for several years—time to understand the evidence needed and design the OR study, prospectively conduct an assessment or evaluation of a service-delivery intervention, and then time to support the health system with institutionalization and scale-up of the organizational changes suggested by the OR findings.

WHO GUIDANCE

WHO guidance will be critical to shaping country policy in many settings and is an essential step toward inclusion on WHO's Model List of Essential Medicines and for launching the prequalification process. WHO is planning to establish a Guideline Development Group by the end of 2012, with a target of having guidance ready for publication soon after the first licensure decision on 1 percent tenofovir gel. The detail and specificity of guidance that can be issued depends on the extent of evidence available to inform that guidance. WHO anticipates that the Guideline Development Group will agree on a limited number of critical questions that need to be answered in order to issue initial policy guidance. These questions can also be used to inform priorities for operations and implementation research that needs to be completed in time for the results to be reflected in the guidance.

WHO uses the **Grading of Recommendations Assessment, Development, and Evaluation (GRADE)** approach to review and weigh the evidence on which the guidance is based. It rates the quality of evidence on a number of parameters (study design, risk of bias, completeness of follow-up, imprecision, inconsistency, indirectness, and the magnitude of the effect), and grades the strength of recommendations (high, moderate, low, very low). In this system, evidence from randomized controlled trials is initially rated higher than evidence from observational studies, but the factors mentioned above are used to increase or decrease the quality of evidence scores. This approach, initially developed to assess clinical evidence, presents challenges with respect to incorporating evidence from OR. Randomized controlled trials are generally inappropriate designs for operations research for reasons that include: the practical and ethical challenges with random assignment, large sample sizes, and controlled implementation; and experimental conditions that are unlike routine service settings. But OR has greater external validity and addresses key policy questions necessary to inform guidance and country policies. It is important to note that WHO normative guidance addresses policy questions, such as whether a particular product or policy should be introduced into programs, and if so how, based on a wider assessment of risks, costs, and opportunity costs. This is distinct from the role of national regulatory authorities which assess safety and efficacy of a new product in order to grant market authorization and thus allow the product to be marketed within their jurisdiction.

The **GRADE "PICOT" (Population, Intervention, Comparison or Control, Outcome, and Time)** approach is designed to clearly define the questions for which evidence is systematically compiled and assessed. Policy questions to be addressed through the PICOT approach often have very limited information to support a recommendation, particularly for new products for which there is no, or limited, programmatic experience. But operations research that addresses questions on how to deliver a gel or ring safely and consistently, user preferences for different HIV prevention products, and identifying niche(s) where the product will be used effectively and have the greatest acceptability and impact would be very valuable to inform guidance. The framework and approaches WHO is currently developing for oral PrEP demonstration projects may be useful for framing OR on gels and rings, and staff at WHO and others interested in microbicide OR and implementation should stay apprised of these efforts. Experience with developing operations research and policy guidance with oral PrEP will also inform research on introduction of gels and rings.

PRIORITY TOPICS, SELECTED QUESTIONS, AND EXPERT FEEDBACK

Participants identified a number of priority topics for operations research both prior to and during the consultation. Much of the discussion focused on models for service delivery, timing, and the use of proxy products, approaches to conveying partial effectiveness, and bolstering adherence.

Sample questions for expert review

Drawing on the Council's expertise and a review of key tools, reports, and literature (see Appendix 1), Council staff developed a number of questions related to operations research across a range of domains (see boxes in this section for select questions and Appendix 2 for the full survey):

- Service delivery models
- Providers
- HIV testing and retesting
- Potential resistance
- Adherence
- Vaginal ring–specific issues
- Vaginal gel–specific issues
- User perspectives and education
- Program costs

These questions were sent to participants prior to the meeting, and participants were asked to rate the questions by level of importance (high, medium, low) and to indicate when research could or should be initiated to address the issue (actionable now, or after a product is approved and available). Responses received were compiled prior to the meeting and presented to meeting participants for an overall sense of priorities and to help jump-start the discussion and debate.

Most items were rated "high" to "medium" priority, with some ranked "high" but not actionable now. With regard to timing, for many questions it was difficult to make clear distinctions as to when a question could and should best be explored. For a number of topics, research conducted while clinical trials are ongoing could yield important findings and insights, which could then inform additional work or research in more routine service settings. The time between demonstration of clinical efficacy and formal approval and/or widespread availability may be particularly fruitful for operations research to inform program design and implementation.

Priority areas

Priority questions focused primarily on identifying appropriate service-delivery models and approaches for reaching different potential user groups, including the types of program entry points (such as reproductive health, antenatal care, HIV counseling and testing, school-based, etc.). Other priorities concerned related service issues such as the level of provider who could safely and appropriately deliver ARV-based prevention products, the kind of medical monitoring that would be required, and the feasibility and need for monitoring potential resistance. It will also be important to understand the implications of periodic HIV testing (for screening for initiating product use as well as for ongoing monitoring of HIV status) on acceptability and uptake among users, providers, and the health system. Recognizing the important role that providers play in influencing policy as well as services, provider knowledge and attitudes were also seen as important. Whereas some issues related to providers can be addressed through research, work in this area will also involve education and training.

Select OR Questions

Service Delivery Models, Programs, Services

- What service model(s) or package is most effective for reaching key populations? Under what conditions? Which populations?
- Which program entry points would be most effective to deliver gel/ring (e.g., RH/FP, ANC, counseling and testing services, primary health care, school health, private sector, etc.)?

Providers: Type, Level, Training

- What cadre(s) (nurse, clinical officer, health worker) of providers is needed to ensure appropriate counseling, provision, testing, resupply, and follow-up?
- What are providers' attitudes and beliefs around ARV-based prevention in general and gel/ring in particular? How can these be influenced to facilitate successful introduction?

HIV Testing and Retesting

- What are the implications of the need for periodic HIV testing on product acceptability and uptake among users, providers, and health systems?
- What are the acceptability and feasibility of different HIV screening and testing approaches to: Clients? Providers? The service site? The health system overall?

Potential Resistance (understanding, minimizing, managing)

- How can potential drug resistance be determined, minimized, and managed in routine services?
- What is the realistic risk of resistance with use of ARV-containing gels and rings?

Participants also identified priorities related to product adherence as well as specific topics relevant to gel and to rings. It has been challenging to maintain and to measure adherence in microbicide trials, and developing and testing approaches to bolstering adherence out-

Select OR Questions (con't)

Adherence: Optimizing and Measuring

- What strategies or combination of strategies (counseling, communications, mobile technologies) are effective for supporting and bolstering adherence among users?
- What are feasible approaches to measuring or assessing adherence under routine service conditions?

Vaginal Ring–Specific Issues

- How can ring service provision be proactive in supporting women's use of the ring, including helping women understand and manage potential expulsions?
- Given that the vaginal ring is not coitally dependent and does not require daily action, what are the implications for adherence, use, user satisfaction?

Vaginal Gel–Specific Issues

- How will the amount of gel provided to users at each visit be determined? Will initial and resupply visits take place at the same location?
- What are the storage implications for gel at the service-delivery site? For the user? For logistics and supply systems?

User Perspectives and Education

- What do women know about ARV-based prevention? What are their views about the gel/ring? What are their partners' views?
- How can the gel/ring's partial effectiveness best be communicated to users?

Program Costs

- What are the anticipated (or likely) product, service, and program costs? Who is expected to pay for these costs?
- What implications do different program models and scenarios have for cost?

side of trials was seen as a clear priority, though the timing is uncertain. Overall, there is less information from trials on the ring than gel, and technology-specific priorities focused on supporting women to understand and use the ring, as well as the implications of a sustained-release method for adherence, use, and user satisfaction. For gel, the priorities were somewhat more instrumental, such as what amount to provide at each visit, storage for users and the health system, and the implications of switching from prefilled to user-filled applicators.

Priorities for user perspectives and education centered around how best to communicate partial effectiveness, and specific counseling requirements for initial adoption and ongoing use/resupply of gel and rings. Finally, the cost implications of different service models, as well as who will pay for the product and programs, were seen by some as a priority. Those issues that surfaced throughout the meeting are discussed in more detail in the following sections.

Populations, service types, and service settings: Weaving it together

Determining which service-delivery settings would be most appropriate and feasible to reach different user groups—the heart of operations research—was a main theme throughout the consultation. Priority user groups would be determined by the specific epidemic in a given setting, as would available services on which to build. For more specific discussions, participants broke into two groups to try to define OR studies and begin to map out study designs using the PICOT framework. With some differences, both groups proposed and worked through similar broad study outlines to explore different dimensions of feasibility, acceptability, cost, and reach of building on existing services to deliver the gel and/or ring to specific user groups.

- **Population**: Relevant population groups would be determined by the nature of the epidemic in a given setting, and the small groups discussed several possible populations for initial OR studies. For example, married women in Kenya and young women in South Africa were both seen to be likely user groups for ARV-based prevention technologies. Most participants felt that initial OR studies could and should be focused in the communities that hosted gel or ring trials. While located in trial communities, OR studies should not be limited to trial participants and, depending on their design, should generally not take place in trial clinics.
- **Intervention**: Priority interventions would focus on different packages of services that include HIV testing and retesting with product supply and resupply (for either ring or gel). These services would be delivered in different settings such as family planning/reproductive health services, HIV testing services, and possibly school-based service points.
- **Comparison**: The studies could be designed to compare different service intervals (for example providing the same service every three months versus every six months) or different service types.
- **Outcome**: Outcomes could include retention in services, adherence, acceptability, and/or cost. One group discussed the emergence of drug-resistant virus as a research priority. Some aspects of resistance could be explored through OR while others would call for clinical research. Priority "nested" studies to investigate specific issues within the context of broader OR efforts could include models for testing, counseling, and information provision, and challenges to logistics or supply-chain management.
- **Time**: The proposed timeframe varied from one to two years, depending on the specific intervention. Some participants argued for a timeframe longer than one year given that retention in microbicide gel trials dropped off after a year.

Timing: When to initiate what types of research

It can be difficult to clearly distinguish when operations research is most appropriate and fruitful for many issues. Some topics—for example, participants' understanding of partial effectiveness—may lend themselves to research in the context of clinical trials, either as a formal part of the trial or an ancillary study. However, findings from studies that employ the participants, clinic staff, and resources from trials may have limited relevance for more routine service settings. Other priority issues, such as testing different approaches to bolstering adherence, may not be possible within randomized controlled clinical trials where service interventions need to remain consistent across comparison groups. Studies under more routine service settings may not be feasible for products that are not yet licensed in a country, though this may be possible in some settings under a research designation. Ideally many issues could be explored in clinical trials and ancillary studies, and then further refined through operations research in pre-introductory and early rollout phases. However, resource constraints may limit such a phased approach. The tension between needing information relevant to implementation in routine service settings, and the limitations on conducting research in such settings with products that are not yet licensed, will remain.

Proxy products: What can we learn from proxies and how can this knowledge be applied?

Most OR is conducted with available products, and the discussion returned repeatedly to the challenging issue of conducting operations research for products under development. Both tenofovir gel and the dapivirine ring will be strictly controlled until they are licensed and approved by national regulatory authorities. While it may be possible to conduct some studies with proxy products, there was considerable debate about the value of research with proxy products (for example, the contraceptive vaginal ring or sexual lubricants) for informing service design, logistics, and other aspects of delivering ARV-containing microbicide products. While some participants felt this approach would yield valuable information about product introduction and delivery, others noted that the differences—for example in service components (such as HIV testing) and motivation of users and providers (to use sexual lubricants compared with tenofovir gel for HIV prevention)—would be so significant that it would be difficult to garner useful lessons for microbicide introduction. Given the publicity around tenofovir gel in South Africa, for example, it could even be misunderstood that the lubricant *is* tenofovir gel, which could cause confusion and might even put women at risk. This issue was not clearly resolved; proxy research may be useful under specific conditions and in different settings, but the implications need careful consideration.

Partial effectiveness: What and how to convey?

A great deal of discussion surrounded the importance and complexity of conveying partial effectiveness to users and policymakers. Generally, participants agreed that shifting both the language and concept from "prevention" to "risk reduction" is important as it may allow and indeed force a rethinking of the concept of "partial effectiveness" and how it can be conveyed in a more affirmative and accurate manner. Such research could draw on other examples of interventions that reduce but do not eliminate risk (such as immunization or seat belts). A useful step would be to review how partial effectiveness has been explained (and understood) in trials to date, and use this information to develop additional research on partial effectiveness, including context specific terminology and concepts, outside of trial populations.

Gels and rings: Shared contexts, unique products

Recognizing the different product attributes and use dynamics between gels and rings, participants broke into two groups to discuss and identify priority research particular to each technology. Given that a number of candidate microbicide gels have been developed and tested in Phase 3 trials, much more data and experience with gels exists. Much of the discussion focused on contextual issues: identifying settings, populations, and individuals who are at risk and thus could benefit most from the gel; how to ensure that the gel is not stigmatized through association with risk groups or behaviors; the possibility of positioning the gel for use in intimate partnerships; and innovative approaches to balancing the need for monitoring with ease of access and ensuring women have an adequate supply including the use of smart cards, SMS, or other electronic approaches. Priority topics for rings include whether women would choose a ring if they were not having sex regularly; the reasons women remove rings, and what is done with the ring when it is taken out; and how to convey the impact of imperfect use on the ring's effectiveness.

Bolstering adherence: How to do it? And then, how to measure it?

Supporting and measuring adherence has been a significant challenge in clinical trials, and it is not known whether adherence will be more or less difficult in ongoing use of proven products. While a great deal of thought and effort has gone into improving approaches to *measuring* adherence, relatively less has been invested in evaluating counseling and strategies for *improving* adherence. Several discussions centered on approaches to bolstering adherence and whether different approaches could be compared in the context of a clinical trial as a nested study. Given the complexity of implementing trials and keeping variation to a minimum, such adherence studies may not be feasible until bridging or pre-introduction studies. One participant noted that specific strategies for improving adherence efforts in trials have not been rigorously evaluated and that doing so may be a productive initial step.

Other cross-cutting issues: Developing champions, civil society engagement

During the consultation's lively and wide-ranging discussions, a number of important issues surfaced that, while critically important, do not lend themselves to operations research per se. For example, discussion returned repeatedly to the best ways to engage providers, who need to be informed about research on gels and rings and brought on board as champions. Similarly, community and advocacy groups offer important perspectives to inform preparation for product introduction and could press governments and donors to invest in new prevention approaches for women. However, appropriately timing such professional and community engagement needs to balance ensuring that key constituencies are informed, and feel informed, without potentially raising expectations too soon and without a clear plan of action.

Defining the market, estimating demand, and understanding market segmentation

While not explicitly discussed during the operations research consultation, product developers working to make tenofovir gel available outlined several critical issues related to estimating and defining the market and reaching users with the product. The coalition of groups that has developed and tested tenofovir gel has come primarily from the public and philanthropic sectors driven by a public health imperative. As the product moves through advanced clinical testing, these efforts are shifting to estimating and defining the market for tenofovir gel to inform manufacturing, investment, and pricing scenarios. Such efforts concern identifying potential user groups in different contexts and then more precisely estimating the uptake and use of the gel to balance building demand with ensuring adequate supply to meet that as yet undefined demand. At the same time, as a product that will likely be subsidized and provided chiefly through the public sector, efforts to provide tenofovir gel will depend on programs developed, funded, and implemented through the public health sector, and interest and commitment to this needs to be understood and to the extent possible, quantified.

LOOKING AHEAD AND MOVING FORWARD

Developing an operations research agenda takes time and is challenging without defined products, settings, and populations. The OR consultation engaged its diverse participants in grappling with how best to define and prioritize research related to delivering ARV-containing gels and rings for women. The process of developing an OR agenda will continue as clinical data continue to emerge on ARV-containing gels and rings. Useful data and lessons will also emerge from the PrEP demonstration projects now being designed and implemented, and it will be important to ensure that some of those projects are developed with an eye to also informing introduction of gels and rings.

Ultimately, the OR agenda for new women-centered prevention will need to be defined by key stakeholders within the framework of specific health systems and epidemics. Given the timeframe for ongoing clinical research and new approaches like medical male circumcision and PrEP that have emerged in the last several years, ARV-containing gels and rings will be introduced as an element of combination prevention. As such, new products will need to be examined and understood within the range of prevention options available. While developing and implementing an OR agenda is a crucial part of preparing for new product introduction, ultimately programs will need to move forward without every question answered. This is and will continue to be a challenging and dynamic process.

APPENDIX 1
REPORTS AND ARTICLES REVIEWED FOR THE CONSULTATION

Document	Author/Organization	Year
Development and coordination of programmatic research on tenofovir gel	WHO, UNAIDS	2011
Report of a consultation: Preparing for pre-exposure prophylaxis (PrEP) results: From research to implementation http://whqlibdoc.who.int/publications/2010/9789241599795_eng.pdf	WHO	2009
Next steps with 1% tenofovir gel http://www.who.int/reproductivehealth/topics/rtis/WHO_UNAIDS_Next_steps_tenofovir_gel_Ex_report.pdf	WHO, UNAIDS	2008
HIV PrEP: New data and potential use *Topics in Antiviral Medicine* December 2011/January 2012; (19)5.	C. Celum	2011-12
Insights and evidence from product introduction: Lessons for microbicides *Day of dialogue meeting report* http://www.popcouncil.org/pdfs/DoDMicrobicides.pdf	M. Brady and E. McGrory Population Council	2007
Planning for PrEP Report published in *Journal of IAS* 2010; 13:24. http://www.jiasociety.org/content/13/1/24	Kim et al. Georgetown University, Imperial College, Gates Foundation	2009
Microbicide access forum meeting	IPM, USAID, WHO	2007
Microbicide access forum meeting report	IPM, Population Council, USAID, WHO	2008
Microbicide access forum meeting report	IPM, USAID, WHO	2009
Mind the gap: Summary of microbicide access forum	IPM, WHO, UNAIDS, AVAC	2011

Document	Author/Organization	Date
Stakeholder meeting on pre-exposure prophylaxis	WHO, UNAIDS, Imperial College London, London School of Hygiene and Tropical Medicine, and Georgetown University	2011
Packaging PrEP to prevent HIV: An integrated framework to plan for pre-exposure prophylaxis implementation in clinical practice *Journal of Acquired Immune Deficiency Syndromes* 2010; 55(1):8-13.	K. Underhill et al.	2010
Designing HIV/AIDS Intervention Studies: An Operations Research Handbook http://www.popcouncil.org/pdfs/horizons/orhivaidsh-ndbk.pdf	A. Fisher et al. Population Council	2002
What works for women and girls: evidence for HIV/AIDS interventions www.whatworksforwomen.org	J. Gay et al. Open Society Institute	2010
Pre-exposure prophylaxis state of the science: Empirical analogies for research and implementation *Current HIV/AIDS Reports* 2010; 7(4): 201–209. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938422/?tool=pubmed	S.A. Golub, D. Operario and P.M. Gorbach	2010
Microbicide acceptability research: recent findings and evolution across phases of product development *Current Opinion in HIV and AIDS* 2008; 3(5): 581–586.	A. Coly and P. Gorbach	2008

APPENDIX 2
QUESTIONS FOR EXPERT REVIEW

These pages contain the full set of questions sent to participants prior to the meeting for review and prioritization. Council staff reviewed and compiled the feedback to serve as a starting point for the discussions and deliberations at the consultation.

Questions	Timing (1, 2)	Priority (H, M, L)	Comments
I. Service Delivery Models, Programs, Services			
1. What service model(s) or package is most effective for reaching key populations? Under what conditions? Which populations?			
2. Which program entry points would be most effective to deliver gel/ring (e.g., RH/FP, ANC, counseling and testing services, primary health care, school health, private sector, etc.)?			
3. What are the resource requirements of different program delivery approaches?			
4. How do counseling needs for gel/ring fit within counseling needs for other services?			
5. How does providing the new product (gel or ring) affect existing services in terms of client flow, operations, staffing, etc.?			
6. What are the implications of the need for medical monitoring for provider and service type?			
II. Providers: Type, Level, Training			
1. What cadre(s) (nurse, clinical officer, health worker) of providers are needed to ensure appropriate counseling, provision, testing, resupply and follow-up?			
2. What are providers' attitudes and beliefs around ARV-based prevention in general and gel/ring in particular? How can these be influenced to facilitate successful introduction?			
3. What is the lowest level of health care provider suitable to ARV-based gel or ring implementation?			
4. What is the role of supervision in ensuring the fidelity of information/messages and the quality of service provision?			

Questions	Timing (1, 2)	Priority (H, M, L)	Comments
III. HIV Testing and Retesting			
1. What are the implications of the need for periodic HIV testing on product acceptability and uptake among users, providers, and health systems?			
2. What are the acceptability and feasibility of different HIV screening and testing approaches to: Clients? Providers? The service site? The health system overall?			
3. What education strategies are most effective in conveying to users the importance of regular retesting for HIV? Does this correlate with actual retesting?			
4. What are the implications of HIV testing and retesting for cost and cost effectiveness?			
IV. Potential Resistance (understanding, minimizing, managing)			
1. How can potential drug resistance be determined, minimized, and managed in routine services?			
2. What is the realistic risk of resistance with use of ARV-containing gels and rings?			
3. What is the feasibility of monitoring resistance?			
V. Adherence: Optimizing and Measuring			
1. What are the patterns of use and use dynamics under "routine" conditions?			
2. What strategies or combination of strategies (counseling, communications, mobile technologies) are effective for supporting and bolstering adherence among users?			
3. What are feasible approaches to measuring or assessing adherence under routine service conditions?			
VI. Vaginal Ring–Specific Issues			
1. How can ring service provision be proactive in supporting women's use of the ring, including helping women understand and manage potential expulsions?			
2. What are the implications of toileting and hygiene practices for the use of vaginal rings?			
3. What is the feasibility of women (in a given setting) caring for, washing, and storing the ring in a safe, discreet place?			
4. Given that the vaginal ring is not coitally dependent and does not require daily action, what are the implications for adherence, use, user satisfaction?			

Questions	Timing (1, 2)	Priority (H, M, L)	Comments
VII. Vaginal Gel–Specific Issues			
1. How will the amount of gel provided to users at each visit be determined? Will initial and resupply visits take place at the same location? [For specific setting, user groups?]			
2. What are the storage implications for gel at the service delivery site? For the user? For logistics and supply systems?			
3. What are key messages for users around leakage, lubrication, hygiene, douching, and other vaginal practices?			
4. What are the best ways to ensure that clients understand and correctly use the gel? In pre-filled applicators? In user-filled paper applicators?			
VIII. User Perspectives and Education			
1. What do women know about ARV-based prevention? What are their views about the gel/ring? What are their partners' views?			
2. How can the gel/ring's partial effectiveness best be communicated to users?			
3. What are the specific requirements for counseling and user education for gel or ring use? For initial adoption? For ongoing use and resupply?			
4. Will gel and rings be explicitly marketed to different user groups? If so, how will they be identified? If not, how will the different technologies be provided/described as part of a package of prevention?			
IX. Program Costs			
1. What are the anticipated (or likely) product, service, and program costs? Who is expected to pay these costs?			
2. What implications do different program models and scenarios have for cost?			
3. What is the marginal cost of adding the product (gel or ring) to a given program or system?			

APPENDIX 3
CONSULTATION AGENDA

MONDAY, JUNE 18		
9:00 a.m.	Coffee & continental breakfast (provided)	
9:30 – 10:00	Meeting Content and Context	**Martha Brady, Population Council** **David Stanton, U.S. Agency for International Development**
10:00 – 11:00	**Setting the Stage**	**Co-Chairs: Naomi Rutenberg, Population Council** and **Nono Simelela, The Presidency-South Africa**
	What works for HIV prevention for women? A review of the evidence	Fitih Bicha, Futures Group
	What have we learned from other health technologies: How do they work for women?	Martha Brady, Population Council
	Discussion, Q and A	
11:00 – 11:15	*Coffee/tea break*	
11:15 – 12:30	**ARV-based Prevention Products for Women**	**Chair: Elizabeth Bukusi, Kenya Medical Research Institute**
	Overview of clinical trials, product pipelines, and timelines	Manju Chatani-Gada, AVAC: Global Advocacy for HIV Prevention
	Gels and rings: Where are we?	
	Questions and clarification	Joe Romano, Consultant, Bill & Melinda Gates Foundation
	Acceptability of rings and gels	Cynthia Woodsong, International Partnership for Microbicides
	Discussion, Q and A	
12:30 – 1:30	*Lunch (provided)*	
1:30 – 3:00	**Evidence Building**	**Chair: Helen Rees, Wits Reproductive Health and HIV Research Institute**
	Key outstanding issues with tenofovir gel	Tim Farley, Sigma3 Services, World Health Organization Consultant
	WHO guidance: What evidence is needed?	
	Operations research: What it can and cannot do	Ian Askew, Population Council/ Kenya
3:00 – 3:15	*Coffee/tea break*	

3:15 – 5:15	**Review and Generate OR Questions**	**Facilitator: Saiqa Mullick, Population Council/South Africa**
3:15 – 4:00	Presentation of research topics and questions: Feedback from participants	Sam Kalibala, Population Council
	Discussion and vetting of broad OR questions for ARV-based prevention products for women	**Facilitators: Sengeziwe Sibeko and Leila Mansoor**
4:00 – 5:15	ARV-based gels and rings: Small groups • Gel group • Ring group	**Facilitators: Elizabeth Bukusi and Cynthia Woodsong**
	Wrap up and instructions for Day Two	
5:30 p.m.	**Adjourn and reception at Population Council**	

TUESDAY, JUNE 19

8:30 a.m.	Coffee & continental breakfast (provided)	
9:00 –11:00	**Roundup of Questions and Issues**	**Facilitator: Lori Heise, London School of Hygiene & Tropical Medicine**
	Re-cap of Day One	Elizabeth McGrory, Consultant
	Report back: Key questions on gels and rings	Rapporteurs from groups
	Vetting and prioritization	Meeting participants
11:00 – 11:15	*Coffee/tea break*	
11:15 – 12:45	**Marrying Research Questions with Research Designs**	**Facilitators: Avina Sarna, Population Council/India and Ian Askew**
	Group discussion	
12:45 – 2:00	*Lunch (provided)*	
2:00 – 3:00	**Wrap Up and Next Steps**	David Stanton, Martha Brady
3:00 – 5:00	**Optional tour** of Population Council's Center for Biomedical Research (CBR) laboratories at Rockefeller University (off-site)	CBR Staff

APPENDIX 4
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